SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

One-Alpha 2 microgram/ml injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfacalcidol 2 micrograms/ml

Excipients with known effect:

Ethanol, sodium citrate, propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless liquid in 1 ml one-point-cut amber glass ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

metabolism due to impaired 1 α-hydroxylation such as when there is reduced renal function.

The main indications are:

a) Renal osteodystrophy

b) Hyperparathyroidism (with bone disease)

c) Hypoparathyroidism

d) Neonatal hypocalcaemia

e) Nutritional and malabsorptive rickets and osteomalacia

f) Pseudo-deficiency (D-dependent) rickets and osteomalacia

g) Hypophosphataemic vitamin D resistant rickets and osteomalacia.

4.2 Posology and method of administration

Posology

The dosage of One-Alpha Injection is the same as for One-Alpha in its oral presentations.

Initial dose for all indications:

Adults and children over 20 kg bodyweight: 1 microgram/day

Elderly: 0.5 microgram/day

Neonates and premature infants: 0.05-0.1 microgram/kg/day

Children under 20 kg bodyweight: 0.05 microgram/kg/day

The dose of One-Alpha should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response.

Indices of response include plasma levels of calcium (ideally corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Maintenance doses are generally in the range of 0.25 to 1 microgram per day.

When administered as intravenous injection to patients undergoing haemodialysis the initial dosage for adults is 1 microgram per dialysis. The maximum dose recommended is 6 micrograms per dialysis and not more than 12 micrograms per week. The injection should be administered into the return line from the haemodialysis machine at the end of each dialysis.

(a) Renal bone disease:

Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to One-Alpha. Other therapeutic measures may be indicated.

Before and during treatment with One-Alpha, phosphate binding agents should be considered to prevent hyperphosphataemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

(b) Hyperparathyroidism:

In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, pre-operative treatment with One-Alpha for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia, One-Alpha should be continued until plasma alkaline phosphatase levels fall to normal or hypercalcaemia occurs.

(c) Hypoparathyroidism:

In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with One-Alpha. Severe hypocalcaemia is corrected more rapidly with higher doses of One-Alpha (e.g. 3-5 micrograms) together with calcium supplements.

(d) Neonatal hypocalcaemia:

Although the normal starting dose of One-Alpha is 0.05-0.1 microgram/kg/day (followed by careful titration), in severe cases, doses of up to 2 microgram/kg/day may be required. Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase approximately 7.5 times above the adult range indicates active disease.

(e) Nutritional and malabsorptive rickets and osteomalacia:

Nutritional rickets and osteomalacia can be cured rapidly with One-Alpha. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of One-Alpha.

(f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:

Although large doses of parent vitamin D would be required, effective doses of One-Alpha are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

(g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:

Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with One-Alpha at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

Method of administration

One-Alpha Injection should be administered intravenously as a bolus over approximately 30 seconds. Shake the ampoule for a minimum of 5 seconds before use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypercalcaemia, metastatic calcification.

4.4 Special warnings and precautions for use

During treatment with One-Alpha, serum calcium and serum phosphate levels should be monitored regularly especially in children, patients with renal impairment and patients receiving high doses. PTH, alkaline phosphatase and calcium phosphates should be monitored as clinically indicated.

Hypercalcaemia might appear in patients treated with One-Alpha. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. Signs of hypercalcaemia are muscle and bone pain, muscle weakness, confusion, dehydration, anorexia, fatigue, nausea and vomiting, constipation, polyuria, sweating, headache, polydipsia, hypertension and somnolence.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). One-Alpha may then be restarted at a reduced dose (half the previous dose) with monitoring of calcium.

Prolonged hypercalcaemia may aggravate arteriosclerosis, cardiac valve sclerosis or nephrolithiasis and therefore prolonged hypercalcaemia should be avoided when One-Alpha is used in these patients. Transient or even long-lasting deterioration of kidney function has been observed. One-Alpha should also be used with caution in patients with calcification of pulmonary tissue as this may result in cardiac disease.

In patients with renal bone disease or severely reduced renal function, a phosphate binding agent could be used simultaneously with alfacalcidol to prevent increased serum phosphate and potential metastatic calcification.

One-Alpha should be used with caution in patients with granulomatous diseases such as sarcoidosis where the sensitivity to vitamin D is increased due to increased hydroxylation activity.

Concurrent use of digitalis glycosides in the presence of hypercalcaemia due to vitamin D administration increases the potential for cardiac arrhythmias.

One-Alpha solution for injection contains up to 160 mg ethanol per dose (corresponding to 4 micrograms of alfacalcidol), which is equivalent to 10 vol%. The amount of ethanol in each dose of One-Alpha is equivalent to 4 ml beer or 1.7 ml wine. The small amount of ethanol in One-Alpha will not have any noticeable effect.

One-Alpha solution for injection contains 0.14 mmol sodium per dose (corresponding to 4 micrograms of alfacalcidol). Products containing less than 1 mmol sodium (23 mg) per dose are considered essentially ‘sodium-free’.

One-Alpha solution for injection contains 415 mg propylene glycol per ml which is equivalent to 20.75 mg/kg/day (corresponding to 0.1 micrograms/kg/day of alfacalcidol). Caution should be exercised in children less than 4 weeks of age, in particular if the child is given other medicines that contain propylene glycol or alcohol.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Thiazide diuretics and calcium containing preparations</u>

Concurrent use of thiazide diuretics or calcium containing preparations may enhance the risk of hypercalcaemia. Calcium levels should be monitored.

Other vitamin D containing preparations
Concurrent use of other vitamin D containing preparations may enhance the risk of hypercalcaemia. Use of multiple vitamin D analogues should be avoided.

Anticonvulsants
Anticonvulsants (e.g. barbiturates, phenytoin, carbamazepine or primidone) have enzyme-inducing effects resulting in an increased metabolism of alfacalcidol. Patients taking anticonvulsants may require larger doses of One-Alpha.

Magnesium-containing antacids
Absorption of magnesium-containing antacids may be enhanced by One-Alpha, increasing the risk of hypermagnesaemia.

Aluminium-containing preparations
One-Alpha may increase the serum concentration of aluminium. Patients taking aluminium containing preparations (e.g. aluminium hydroxide, sucralfate) should be monitored for signs of aluminium related toxicities.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of alfacalcidol in pregnant women. Studies in animals have shown reproductive toxicity at high doses.

Therefore, One-Alpha is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

Although it has not been established, it is likely that increased amounts of 1,25-dihydroxyvitamin D will be found in the milk of lactating mothers treated with One-Alpha. This may influence calcium metabolism in the infant.

Consequently, breast-fed infants of alfacalcidol-using mothers should be monitored closely for hypercalcaemia.

Fertility

There are no clinical studies on the effect of One-Alpha on fertility. A pre-clinical study did not show an effect on fertility in rats.

4.7 Effects on ability to drive and use machines

Alfacalcidol has no or negligible direct influence on the ability to drive and use machines. However, the patient should be informed that dizziness may occur during treatment and take this into account while driving or using machines.

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and spontaneous reporting.

The most frequently reported undesirable effects are various skin reactions such as pruritus and rash, hypercalcaemia, gastrointestinal pain/discomfort and hyperphosphataemia.

Renal failure has been reported post-marketing.

Undesirable effects are listed by MedDRA system organ class (SOC) and the individual undesirable effects are listed starting with the most frequently reported one. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common ≥1/10

Common ≥1/100 to < 1/10

Uncommon ≥1/1,000 to <1/100

Rare ≥1/10,000 to <1/1,000

Very rare <1/10,000

Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders	
Common:	**Hypercalcaemia** **Hyperphosphataemia**
Psychiatric disorders	
Not known:	**Confusional state**

Nervous system disorders	
Uncommon:	**Headache**
Rare:	**Dizziness**
Gastrointestinal disorders	
Common:	**Abdominal pain and discomfort**
Uncommon:	**Diarrhoea** **Vomiting** **Constipation** **Nausea**
Skin and subcutaneous tissue disorders	
Common:	**Rash*** **Pruritus** ***Various types of rash such as erythematous, maculo-papular and pustular have been reported**
Not known:	**Urticaria**
Musculoskeletal and connective tissue disorders	
Uncommon:	**Myalgia**
Renal and urinary disorders	
Common:	**Hypercalciuria**
Uncommon:	**Nephrolithiasis/ Nephrocalcinosis**
Not known:	**Renal impairment (including acute renal failure)**
General disorders and administration site conditions	
Uncommon:	**Fatigue/asthenia/malaise** **Calcinosis**

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Excessive intake of One-Alpha may lead to the development of hypercalcaemia, however, the effect is reversed rapidly on withdrawal.

In severe cases of hypercalcaemia general supportive measures should be undertaken: Keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal function indices, assess electrocardiographic abnormalities, especially in patients using digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, ATC code A11CC03.

Alfacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin D. This is the metabolite of vitamin D which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of One-Alpha* and 1,25-dihydroxyvitamin D are very similar.

Impaired 1α-hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and vitamin D dependent rickets. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of One-Alpha*.

The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of One-Alpha* is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

In patients on regular haemodialysis administration of doses between 1 - 4 micrograms of intravenous 1 α-hydroxyvitamin D_3 resulted in increased levels of 1,25 dihydroxyvitamin D. Formation of 1,25 dihydroxyvitamin D_3 occurred within

1 hour after intravenous 1 α -hydroxyvitamin D_3 and peak concentrations were reached between 2 and 5 hours. Elimination half life of the formed 1,25 dihydroxyvitamin D was between 14 and 30 hours.

5.3 Preclinical safety data

The non-clinical toxicity of alfacalcidol is attributed to the known vitamin D-effect of calcitriol on calcium homeostasis, which is characterised by hypercalcaemia, hypercalciuria and eventually soft tissue calcification.

Alfacalcidol is not genotoxic.

No specific effects of alfacalcidol on fertility or behaviour of the offspring were noted in rats and rabbits. In terms of embryo-fetal development, fetal toxicity (post-implantation loss, lower litter size and lower pup weight) was observed at doses high enough to cause toxicity in the dams. High doses of vitamin D are known to be teratogenic in experimental animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid
Ethanol
Sodium citrate
Propylene glycol
Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at 2 to 8°C.

Keep the ampoule in the outer carton in order to protect it from light.

6.5 Nature and contents of container

10 x 0.5 ml amber glass ampoules.

10 x 1.0 ml amber glass ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 July 1991

Date of latest renewal: 11 November 2005

10 DATE OF REVISION OF THE TEXT

11/04/2022